Unprecedented use of ^{29}Si NMR spectroscopy for a convenient determination of enantiomeric excesses of chiral α-*C*-silylated amines and alcohols†

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The use of routine refocused-decoupled INEPT ^{29}Si NMR spectroscopy, in the presence of the chiral lanthanide shift reagent Eu(tfc)$_3$, allows convenient enantiomeric excess determination of chiral α-*C*-silylated amines and alcohols for the first time.

The constant interest in α-*C*-silylated amines, from a synthetic[1] and biological[2] point of view, has led a large number of authors to propose different syntheses for these compounds. Recently we proposed several methods giving access to 1-(trimethylsilyl)alkylamines.[3] One of these consisted of the reduction of acylsilane imines obtained *via* reductive silylation of cyanohydrins.[4]

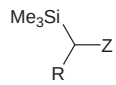
Because of the potential biological interest of these amines and their derivatives, their synthesis in enantiomeric form is of importance. Although the literature provided us with some examples,[5] no synthesis of such chiral primary amines were described before our recent publication.[6] This led us to search for an accurate, reliable and convenient method for measuring the enantiomeric purity of the synthesized amines.

Many new NMR spectroscopic techniques for the determination of ee now exist.[7] We made our first different attempt using ^{1}H and ^{13}C NMR spectroscopy and the chiral auxiliary Eu(tfc)$_3$. We obtained poor separation and the spectra were complicated by the many protons and carbon atoms present in the compound and the lanthanide shift reagent (LSR). We turned next to ^{29}Si NMR spectroscopy, although methods exploiting the chemical shift sensitivity of this nucleus in organosilicon compounds have not so far been reported. Our experiments required the use of a routine polarization transfer technique, the ^{29}Si NMR refocused-decoupled INEPT experiment, based on the INEPT sequence,[8] which allowed us to circumvent the long relaxation time of the silicon atom. The sensitivity of this technique, which depends on the number of coupled protons, was enhanced in the case of trimethysilylated compounds. The refocusing delay time parameter (Δ = 0.02 s) was graphically chosen with the computer program SIMEPT,[9] on the basis of analytical expressions for the theoritical enhancement of decoupled INEPT spectra,[10] in order to obtain optimum enhancement, which depends on delay times. The chiral auxiliary Eu(tfc)$_3$, which converts the mixture of enantiomers into a diastereoisomeric mixture, was directly added into the NMR sample.

We studied racemic amines first. After a few minutes, the decoupled ^{29}Si NMR spectrum showed two signals of approximately the same intensity due to rapid exchange at equilibrium between the diastereoisomeric adducts and the parent racemic mixture of stereoisomers. The shift of these signals from the signal of the starting racemic mixture increased with the quantity of the europium salt added, as was the broadening of the signals. Best results were obtained with an LSR : substrate molar ratio in the 3–10% range. The results shown in the Table 1 (compounds **1**–**3**) proved the validity of the method.

In order to show that this method could be valuable for other α-*C*-silylated compounds, we also tested racemic α-*C*-silylated alcohols (Table 1, compounds **4**–**6**), synthesized by reduction of the parent acylsilanes obtained by standard methods.[11]

Table 1 Enantiomeric ratios measured for racemic α-*C*-silylated amines and alcohols

Compound		Z	R	LSR/ mol%	$\Delta\delta$ (ppm)[a]	Diastereoisomeric ratio[b]
	**1**	NH_2	Pr	6.2	0.021	50.7 : 49.3
	2	NH_2	C_6H_{11}	8.0	0.069	50.2 : 49.8
	3	NH_2	Bu^t	5.5	0.032	50.5 : 49.5
	4	OH	Me	6.2	0.031	50.3 : 49.7
	5	OH	Pr^i	3.2	0.138	50.1 : 49.9
	6	OH	Ph	10.0	0.031	50.3 : 49.7

[a] In $CDCl_3$ at 25 °C. ^{29}Si NMR chemical shift and separation have been shown to be solvent, substrate, LSR concentration and temperature dependent. See ref. 12. [b] Based on the integration of the ^{29}Si NMR resonances (±1%).

The ratios obtained from ^{29}Si NMR integrations confirmed that the parent mixtures were racemic and showed that this method was valuable also in these cases. However, failure was observed with α-*C*-silylated chloroalkanes, probably because the lower basicity of the chlorine atom stops the molecule complexing with Eu(tfc)$_3$.

An example of the results obtained using this technique is shown in Fig. 1.

Non-racemic mixtures of 1-(trimethylsilyl)butylamine **1** were obtained *via* asymmetric reduction of butyryltrimethylsilane imine under various conditions.[6] The NMR technique was applied to the determination of the ee of these mixtures (see example in Fig. 2) and the results were in good agreement with the mesured specific rotations (Table 2).

In summary, the $\Delta\delta_{Si}$ values of α-*C*-silylated amines and alcohols, obtained from routine refocused-decoupled INEPT experiments in the presence of Eu(tfc)$_3$, indicate that the chemical shift sensitivity of the silicon nucleus allows the determination of ee. This technique is possible because the observed silicon nucleus is close to the chiral and the complexation centers. From a practical point of view, this new and simple method (a single signal in the spectrum is converted into a double one) will be useful in the frame of the asymmetric synthesis of α-*C*-silylated amines and alcohols because it allows a rapid, convenient and accurate determination of the ee.

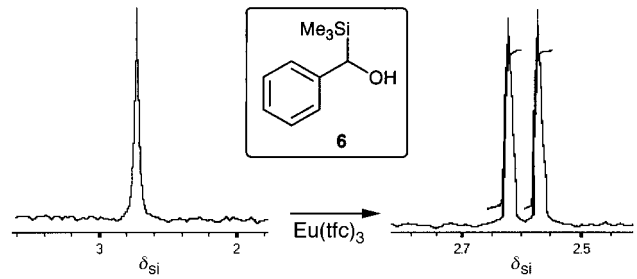


Fig. 1 ^{29}Si NMR spectra of **6** before and after the addition of Eu(tfc)$_3$.

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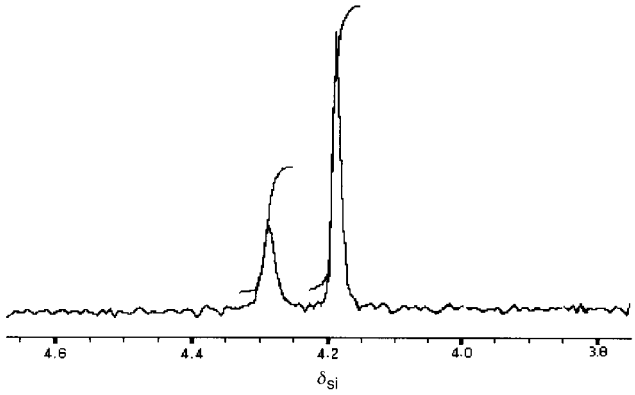

Fig. 2 ^{29}Si NMR spectra of enantioenriched 1-(trimethylsilyl)butylamine **1** after the addition of Eu(tfc)$_3$ (39% ee) (ref. 13).

Table 2 Comparison of experimental specific rotations and ees for various non-racemic mixtures of 1–(trimethylsilyl)butylamine

$[\alpha]_D^{20}$ (MeOH)	Ee (%)
+3.8	39
+2.9	31
+3.5	36
+6.1	60

Further applications of this novel technique are under investigation.

Notes and references

1 See for examples: R. Katritsky and S. Sengupta, *Tetrahedron Lett.*, 1987, **28,** 5419; V. Snieckus, *Pure Appl. Chem.*, 1990, **62,** 671 and references cited therein; J. Lasarte, C. Palomo, J.-P. Picard, J. Dunoguès and J.-M. Aizpurua, *J. Chem. Soc., Chem. Commun.*, 1989, 72; C. Palomo, J.-M. Aizpurua, J.-M. Garcia, J.-P. Picard and J. Dunoguès, *Tetrahedron Lett.*, 1990, **31**, 1921; O. Tsuge, S. Kanemasa, T. Yamada and K. Masuda, *J. Org. Chem.*, 1987, **52**, 2523; A. Padwa and W. Dent, *J. Org. Chem.*, 1987, **52**, 235.

2 See for examples: R. J. Fessenden and M. D. Coon, *J. Med. Chem.*, 1964, **7**, 561; M. Kurono, R. Unno, Y. Matsumoto, Y. Kondo, T. Mitani, T. Jomori, H. Michishita and K. Sawai, *Eur. Pat. Appl.* EP 288,002 1988 (*Chem. Abstr.*, 1989, **110**, 75808); M. Kurono, T. Suzuki, T. Suzuki, K. Hirooka, Y. Matsumoto, H. Ozawa and K. Sawai, *Eur. Pat. Appl.* EP 299,495 1989 (*Chem. Abstr.*, 1989, **111**, 7217); R. Tacke, R. Niedner, J. Frohnecke, L. Ernst and W. S. Sheldrick, *Liebigs Ann. Chem.*, 1980, 1859; R. B. Silverman and G. M. Banik, *J. Am. Chem. Soc.*, 1987, **109**, 2219. G. M. Banik, R. B. Silverman, *J. Am. Chem. Soc.*, 1990, **112**, 4499.

3 T. Constantieux, S. Grelier and J.-P. Picard, *Main Group Met. Chem.*, 1997, **20**, 503.

4 T. Constantieux and J.-P. Picard, *Organometallics*, 1996, **15**, 1604.

5 See for example: R. E. Gawley, G. Hart, M. Goicoechea-Pappas and A. Smith, *J. Org. Chem.*, 1986, **51**, 3076; R. E. Gawley, G. C. Hart and L. J. Bartolotti, *J. Org. Chem.*, 1989, **54**, 175; H. Hengelsberg, R. Tacke, K. Fritsche, C. Syldatk and F. Wagner, *J. Organomet. Chem.*, 1991, **415**, 39; S. T. Kerrick and P. Beak, *J. Am. Chem. Soc.*, 1991, **113**, 9708; D. J. Gallagher, S. T. Kerrick, and P. Beak, *J. Am. Chem. Soc.*, 1992, **114**, 5872; D. J. Gallagher, S. Wu, N. A. Nikolic and P. Beak, *J. Org. Chem.*, 1995, **60**, 8148; C. Barberis and N. Voyer, *Tetrahedron Lett.*, 1998, **39**, 6807.

6 F. Fortis and J.-P. Picard, *Tetrahedron: Asymmetry*, 1998, **9**, 3455.

7 See for example: J. A. Dale, D. L. Dull and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543; R. Wu, G. Hernandez, J. D. Odom, R. B. Dunlap and L. A. Silks, *Chem. Commun.*, 1996, 1125; P. Lesot, D. Merlet, A. Loewenstein and J. Courtieu, *Tetrahedron: Asymmetry*, 1998, **9**, 1871; D. Merlet, A. Loewenstein, W. Smadja, J. Courtieu and P. Lesot, *J. Am. Chem. Soc.*, 1998, **120**, 963.

8 G. A. Morris and R. Freeman, *J. Am. Chem. Soc.*, 1979, **101**, 760.

9 J.-C. Lartigue, M. Pétraud, M. Harket, B. De Jéso and M. Ratier, *Comput. Chem.*, 1996, **20**, 219.

10 K. V. Schenker and W. Von Philipsborn, *J. Magn. Reson.* 1985, **61**, 294.

11 Compound **4** from acetyltrimethylsilane (BH_3, THF, 80%): J. A. Soderquist and A. Hassner, *J. Organomet. Chem.*, 1978, **156**, C12; Compound **5** from isobutyryltrimethylsilane ($LiAlH_4$, 75%): J.-P. Picard, J.-M. Aizpurua, A. Elyusufi and P. Kowalski, *J. Organomet. Chem.*, 1990, **391**, 13; Compound **6** from benzoyltrimethylsilane ($LiAlH_4$, 82%): J.-P. Picard, R. Calas, J. Dunoguès, J. Gerval and P. Lapouyade, *J. Org. Chem.*, 1979, **44**, 420.

12 A representative procedure is as follows: 20 mg of the substrate was placed in a 5 mm NMR tube, and 4 cm^3 of dry $CDCl_3$ and Eu(tfc)$_3$ were added. The tube was sealed under nitrogen with cling-film and shaken briskly by hand to ensure complete dissolution. After 30 min, the ^{29}Si NMR spectrum (39.76 MHz) was collected (256 scans) at 300 K on a Bruker Avance DPX 200 MHz spectrometer over a spectral width of 7961 Hz with a repetition delay of 1 s between scans to allow for complete relaxation. INEPT delay time parameters choosen were τ = 0.0357 s and Δ = 0.02 s. Slight line Gaussian multiplication (−0.1 Hz) was applied to aid resolution. The FIDs were Fourier transformed and phased automatically, the same phase corrections being applied for each sample. Integration gave the relative proportions of the diastereoisomeric complexes as listed in Table 1.

13 See Table 1, Experiment 1 in ref 6.

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